A phase diagram of cell-like particles with contact inhibition of locomotion

Bart Smeets, Ricard Alert, Jiří Pešek,
Ignacio Pagonabarraga, Herman Ramon, Romaric Vincent

The regular distribution of neuronal cells, self-healing epithelial monolayers or 3D tumor formation are examples of active-organization of cells in tissues. While cell-substrate and cell-cell adhesions have a widely acknowledged implication in these macroscopic organizations, the role of the cell-specific contact repulsion called contact inhibition of locomotion (CIL) is less clear. In this work, we include these fundamental cellular functions in large scale 2D simulations of cell-like particles. We built a phase diagram which describes within the same unifying framework several of the known multicellular organizations (Figure 1). We provide theoretical scaling laws for transitions such as epithelial-mesenchymal transitions or the dewetting of a 2D epithelium into a 3D agglomerate, which signpost the biophysical pathways available to control these transitions.

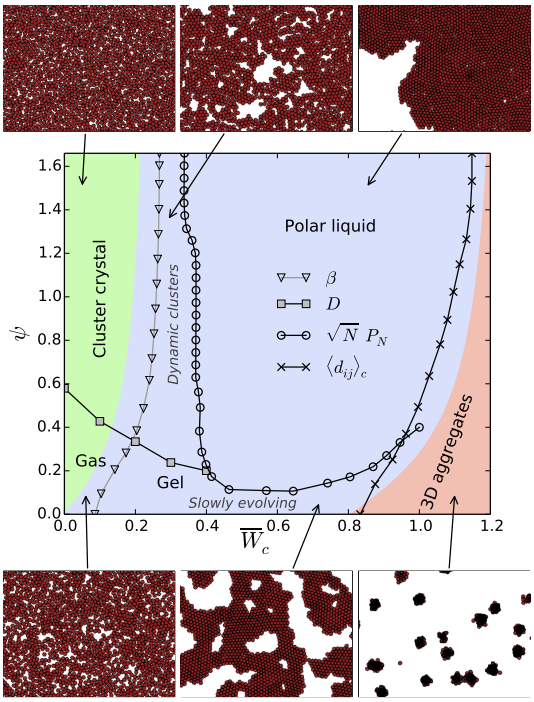

Figure 1: Phase behavior of cell colonies as a function of cell-cell adhesion $\overline{W}_c$ and cell repolarization rate ψ associated to CIL. Colors indicate the predicted regions for non-cohesive (green), cohesive (blue), and overlapped (red) organizations. In addition to capturing these structural transitions, simulations allow to identify dynamically distinct states such as an active gas, a cluster crystal, a gel-like percolated network, dynamic clusters, and an active polar liquid, as illustrated in snapshots.

Our results show how CIL leads to regular cell arrangements, and hinders the formation of cohesive tissues, as well as their extrusion-mediated collapse into 3D aggregates. Self-organized collective cell motion, with tensile intercellular stresses, also emerges from CIL interactions. In addition, we analytically derived an effective CIL-induced cellular repulsion, which yields explicit predictions for transitions between non-cohesive, cohesive, and 3D colonies. Based on experimental observations and parameter estimates, we associate these phases to mesenchymal, epithelial, and 3D tissue phenotypes. Thus, our predictions may have implications for processes in development and cancer that modify the tissue phenotype. In general, our active soft matter approach paves the way towards a physical understanding of multicellular organization and collective cell behavior.